Thank you for the intellectual comments. It is my great honor to answer the problems that Dr Lin suggested and to have such a fruitful discussion.

We agreed with Dr Lin that the impact of body-mass index (BMI) and obesity on the clinical outcomes of the coronary artery disease (CAD) patients treated with percutaneous coronary intervention (PCI) was controversial and the impact of BMI would differ according to the study population and focused clinical events.

According to the suggestion, we analyzed the impact of the BMI category on the short-term (≤1 year) and the long-term (>1 year) clinical outcomes after PCI. As a result, the BMI category was significantly associated with not only the short-term but also the long-term mortality after PCI in our registry. Furthermore, obese subjects tended to have lower risk of cardiovascular death and significantly lower risk of heart failure admission. Because of the small sample size and limited follow-up periods, we could not evaluate the impact of BMI on very long-term (more than 5 years) clinical outcomes after PCI in our registry. Further study is needed to clarify this point. However, a J-shaped relationship between BMI and mortality rate was not seen in the chronic phase after PCI in the follow-up period of our registry.

Next, we would like to answer the question regarding bare metal stent (BMS) and drug-eluting stent (DES) use. In the present study, BMS were implanted in 33%, whereas DES were implanted in 65% of study patients. According to the comments, we divided the patients into the BMS-treated group and the DES-treated group, and analyzed the impact of the BMI category on the long-term mortality, respectively. Kaplan–Meier curves and the log-rank test revealed that obese patients had significantly lower incidences of all-cause death both in the BMS-treated group and the DES-treated group. As Dr Lin mentioned, the obesity-mortality paradox seemed to be attenuated in patients treated with DES. However, we think that this phenomenon is mainly caused by the fact that BMS were selected in patients with acute coronary syndrome, whereas DES were selected in patients with stable angina pectoris in our clinical practice. Dr Lin referred to the work by Wang et al., demonstrating that obese patients had a higher risk for long-term clinical outcomes following PCI with DES [1]. However, the endpoint of this article was the composite of cardiovascular thrombotic events, including cardiac death and non-fatal myocardial infarction, therefore this paper did not evaluate the obesity-mortality (all-cause mortality) paradox after PCI. Moreover, patients with older age, ST-elevation myocardial infarction, severe renal dysfunction, and prior history of revascularization therapy, etc., were excluded in the study by Wang et al. In contrast, our registry included all CAD patients treated with PCI [2], which might account for the differences of the results between our study and those of Wang et al. Considering this point, patient selection and endpoint setting is important when we compare the results of the different studies and discuss the obesity paradox after PCI.

As we described in the original paper, we recognize that our study has several limitations. This study is based on a single center's experience, and the number of study patients was small. Therefore, the results cannot be generalized to all medical centers. As the lean patients were older and had higher frequency of chronic kidney disease, it might be possible that the lean patients had more severe CAD. Further study is required to clarify the association of the severity of CAD and the obesity paradox after PCI.

due to sophisticated patient care and the improved prognosis of CAD patients, the obesity-mortality paradox may be attenuated in future. However, we also believe that the obesity paradox is still applicable to particular subjects with CAD after PCI. We think that it is more important to clarify such patients and to explain the mechanisms of obesity paradox. A causal link between obesity and improved clinical outcomes is biologically plausible. Adipose tissue is increasingly recognized as an active endocrine organ, however, the effects of adipokines on CAD remain unclear. Among patients with heart failure (HF), obese subjects have lower levels of tumor necrosis factor (TNF) and other inflammatory cytokines [3]. Interestingly, increased adipose tissue production of soluble TNF receptors, which is believed to neutralize TNF-α [4] in obese subjects might have a cardioprotective effect in patients with HF. Production of leptin is increased in obese subjects, and leptin has previously been implicated as an independent risk factor for CAD. On the other hand, Momin et al. demonstrated that leptin was a vasoactive peptide in human saphenous vein and internal mammary artery and its action was not nitric oxide or endothelial-dependent [5]. Further study is needed to elucidate the complicated associations between these adipokines and obesity paradox. These fields are really interesting and will clarify the mechanisms of obesity paradox.

We hope that our reply will address the problems that Dr Lin suggested. Once again, we would like to thank you for your intellectual comments. We would be most grateful if we could continue to have such a scientific discussion in future.

References

[1] Wang ZJ, Zhou YJ, Liu YY, Yu M, Shi DM, Zhao YX, Guo YH, Cheng WJ, Nie B, Ge HL, Jia DA, Yang SW, Yan ZX. Obesity and cardiovascular thrombotic events in patients undergoing percutaneous coronary intervention with drug-eluting stents. Heart 2009;95:1587–92.
[2] Kaneko H, Yajima J, Oikawa Y, Tanaka S, Fukamachi D, Suzuki S, Sagara K, Otsuka T, Matsuno S, Funada R, Kano H, Uejima T, Koike A, Nagashima K, Kirigaya H, et al. Obesity paradox in Japanese patients after percutaneous coronary intervention: an observation cohort study. J Cardiol 2013;62:18–24.
[3] Feldman AM, Combes A, Wagner D, Kadakomi T, Kubota T, Li YY, McTiernan C. The role of tumor necrosis factor in the pathophysiology of heart failure. J Am Coll Cardiol 2000;35:537–44.
[4] Mohamed-Ali V, Goodrick S, Bulmer K, Holly JM, Yudkin JS, Coppack SW. Production of soluble tumor necrosis factor receptors by human subcutaneous adipose tissue in vivo. Am J Physiol 1999;277:E971–5.
[5] Momin AU, Melikian N, Shah AM, Grieve DJ, Wheatcroft SB, John L, El Gamel A, Desai JB, Nelson T, Driver C, Sherwood RA, Kearney MT. Leptin is an endothelial-independent vasodilator in humans with coronary artery disease: evidence for tissue specificity of leptin resistance. Eur Heart J 2006;27:2294–9.

Hidehiro Kaneko (MD)*
The Cardiovascular Institute, Tokyo, Japan

* Correspondence to: Department of Cardiovascular Medicine, The Cardiovascular Institute, 3-2-19 Nishiazabu, Minato-ku, Tokyo 106-0031, Japan.
Tel.: +81 3 3408 2151; fax: +81 3 3408 2159.
E-mail address: kanekohidehiro@gmail.com

24 September 2013

Available online 2 November 2013

http://dx.doi.org/10.1016/j.jjcc.2013.09.005